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November 22, 2000

BOX PATENT APPLICATION
Assistant Commissioner
for Patents
Washington, D.C. 20231

Re: Application of **Thomas Sai Ying KO**
entitled "**NOVEL COMPOSITIONS AND METHODS**"
Our Ref: Q-61930

Dear Sir:

Attached hereto is the application identified above including 35 sheets of the specification and claims and 1 page Abstract. The executed Declaration and Power of Attorney will be submitted at a later date.

The Government filing fee is calculated as follows:

Total claims	<u>23</u>	- 20	=	<u>3</u>	x	\$18.00	=	<u>\$54.00</u>
Independent claims								
Base Fee	<u>3</u>	- 3	=	<u>0</u>	x	\$80.00	=	<u>\$0.00</u>
Multiple Dependent Claim Fee								
								<u>\$710.00</u>
								<u>\$270.00</u>
TOTAL FEE							\$1034.00	

The statutory filing fee, in the amount of \$1,034.00, will be submitted at a later date.

Priority is claimed from November 23, 1999, based on Australian Application No. PQ4190. The priority document will be filed at a later date.

The Assistant Commissioner is hereby directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Assistant Commissioner is also hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 and any petitions for extension of time under 37 C.F.R. § 1.136 which may be required during the entire pendency of the

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application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Respectfully submitted,
**SUGHRUE, MION, ZINN,
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Attorneys for Applicant


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NOVEL COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

The present invention relates to a non-aerosol spray-on skin patch composition and methods 5 of using it in improving wound healing, and/or administering a physiologically active ingredient to a patient. The invention also relates to a spray on skin patch drug delivery system. Other aspects of the invention will become apparent from the description that follows.

10 BACKGROUND OF THE INVENTION

Although there are several skin patch compositions available on the market, which can be used for forming a protective film over a wound, they are associated with a number of problems. The spray-on skin patches presently known basically take the form of a water insoluble polymer dissolved in an organic solvent, with an appropriate propellant that will 15 allow it to be applied in an aerosol form. A significant disadvantage with such compositions is that after being applied to the skin and being left to dry a non-porous film structure is formed that prevents the passage across it of gasses or moisture. The failure to allow moisture to move away from the wound results in excess moisture being trapped beneath the film surface causing depredation of the wound, and the possibility of infection.

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It is also problematic that due to delivery via an aerosol means with the aid of a propellant, the spray-on skin patch is applied at a high pressure and can cause pain or discomfort to the patient when applied to a wound area. It has previously not been thought possible to eliminate the propellant from such compositions in order that the composition can be 25 administered under lower pressure, the reason being that it was generally believed the presence of propellant was essential to prevent the clogging of the spraying nozzle through which the composition is applied.

Use of known spray-on skin patch composition has also been demonstrated in the past to 30 allow the growth of microorganisms beneath the film covering that can lead to wound infection as indicated above.

The prevention or treatment of local or topical disease states or conditions of the skin has traditionally used simple non-occlusive delivery systems. These drug delivery systems 35 usually include a volatile and/or non-volatile medium where a composition of the drug and medium is topically applied to the skin, in the vicinity of or directly on the area of skin to be

treated. These delivery systems usually take the form of emulsion, creams, ointments, foams, gels, liquids, sprays and aerosols. Such delivery systems are generally used to treat skin inflammations, fungal and bacterial topical infection, soft-tissue contusions, parasites and topical analgesia. The limitation with this type of delivery system is that systemic drugs 5 are generally not suitable for this type of administration, due to various factors possibly including the short interval of application. Some major problems with the current state of the art relate to a lack of efficacy of systemic drugs because of the low drug flux across the skin, inability to adequately control the rate of drug delivery, or the requirement for a very large application area. Problems with the poor dermal penetration of drugs is that the drug 10 can be easily washed off, or transferred to clothes, other surfaces.

The dermal delivery of drugs may represent one of the oldest form of drug delivery in human history. Resins and animal fats were probably used by humans in early times to treat damage to the skin resulting from injuries and burns. Such substances for local delivery of 15 active substances remained largely unchanged until as late as this century. The concept of transdermal systemic drug delivery was first seriously advocated by Dr Alejandro Zaffaroni, for example, in US patents 3598122 and 3731683 from the early 1970s. Transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances where the drugs are poorly absorbed by traditional 20 routes of delivery, and/or when oral dosing is poorly tolerated or not possible.

Transdermal formulations are however limited. For example, polar drugs tend to penetrate the skin too slowly. Since most drugs are of a polar nature this limitation is significant, as is the fact that many drugs cause irritation at the site of topical application.

25 One common method known for assisting the rate of penetration of drugs across the skin is to increase the thermodynamic activity of the drug. The thermodynamic activity of a drug is proportional to the concentration of the drug and the selection of the vehicle. According to the laws of thermodynamics, the maximum activity of a drug is related to that of the pure 30 drug crystal.

From the 1970s a principal focus of transdermal systemic drug delivery has been, and remains, on transdermal patch devices. These patch devices are like bandages which are attached to the surface of intact skin for prolonged periods of time to allow a desired 35 systemic delivery of a drug or other physiologically active agent. These transdermal patch devices occlude the skin and trap the drug, together with volatiles and vehicle excipients,

between the skin and an outer impermeable backing membrane. The membrane prevents the evaporation or diffusion of vehicle excipients, volatiles and drug into an environment other than the specific target skin site. The prolonged length of time required for transfer of the drug and excipients from the patch into the skin often results in local skin irritation. The 5 irritation is caused by prolonged contact on the skin by the drug, volatiles, vehicle excipients, or the adhesive used to attach the patch device to the skin. The occlusive nature of the patch device also restricts the natural ability of the skin to "breathe", this being uncomfortable and increasing the risk of irritation. With added problems of complex and costly manufacturing processes for transdermal patch devices there is a need for improved 10 transdermal drug delivery systems which allow ease of administration, simple preparation and comparatively low cost preparation.

The thermodynamic activity of a drug can be increased by employing supersaturated systems which give rise to unusually high thermodynamic potentials (Coldman, *et al*, *J. Pharm. Sci.* 58(9):119, 1969). However, topical vehicles relying on supersaturation have the 15 major limitation of formulation instability, both prior to and during application to the skin. As such, they are of limited clinical value within a non-occlusive volatile:non-volatile delivery vehicle, because as soon as the formulation comes into contact with a person's clothing or the like, the drug often precipitates; hence the formulation is no longer 20 supersaturated and any enhanced percutaneous absorption ceases.

Other workers such as Kondo, *et al* (*J. Pharmacobio-Dyn.*, 10:743 1987) who were using supersaturation to achieve enhanced transdermal drug delivery, have relied on the use of anti-nucleating polymers to stabilize the formulation. However, the applied drug 25 formulations stabilized with polymers formed an appreciable surface mass on the skin which remained there over a prolonged duration of many hours, not a few minutes. So, while Kondo advocated the use of a metered spray to deliver these formulations, in reality it would be impossible to obtain a non-occlusive delivery system with a short application time and still maintain a clinically useful transdermal penetration enhancement.

It is accordingly an object of the present invention to provide a spray-on skin patch composition that overcomes some of the problems associated with prior art compositions and systems. Other objects of the present invention will become apparent from the following detailed description.

SUMMARY OF THE INVENTION

According to one embodiment of the present invention there is provided a non-aerosol spray-on skin patch composition comprising:

- (a) at least one substantially water insoluble film forming agent;
- 5 (b) at least one film plasticiser agent;
- (c) at least one water soluble compound; and
- (d) at least one organic solvent;

the composition forming a flexible, porous and physiologically compatible skin patch when sprayed onto skin and allowed to dry.

10

The composition may also include a physiologically active ingredient or pro-drug thereof for application to a wound site.

According to another embodiment of the invention there is provided a spray patch skin 15 delivery composition comprising:

- (a) at least one substantially water insoluble film forming agent;
- (b) at least one film plasticiser agent;
- (c) at least one water soluble compound;
- (d) at least one organic solvent; and

20 (e) one or more physiologically active ingredient or a pro-drug thereof ;
the composition forming a flexible, porous and physiologically compatible skin patch when sprayed onto skin and allowed to dry, and which provides transdermal drug delivery.

According to another aspect of the invention there is provided a spray patch transdermal 25 drug delivery system which comprises at least one physiologically active agent or pro-drug thereof in a water insoluble, porous, film structure containing drug depots.

According to a still further embodiment of the present invention there is provided a method of improving wound healing or administering a physiologically active ingredient to a patient 30 in need of such treatment comprising applying to a wound or to skin of the patient an effective amount of a composition as referred to above.

Other aspects of the invention are described hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising"; will be understood to imply the inclusion of a stated integer or step or group of integers or steps 5 but not the exclusion of any other integer or step or group of integers or steps.

By the term "non-aerosol" it is intended to mean that the composition does not comprise a propellant that will serve to deliver it under pressure. By way of example, the composition may conveniently be applied from a pump-pack type of dispensing container that will utilise 10 the pumped influx of air to force the composition out through a spraying nozzle, under relatively low pressure.

There are several aspects to the invention. In one main aspect the skin patch composition is adapted to be sprayed onto a wound, such as for example a cut, sore, abrasion, burn or other 15 affected part of the skin. In another aspect, a spray patch skin delivery composition is adapted to be applied to normal skin as a means of delivering to or through the skin (transdermally) of the patient a physiologically active ingredient such as systemically active drug, or prodrug thereof. In such cases the spray-on skin patch composition will preferably be delivered/administered in a metered dose.

20

In a first aspect of the invention the composition comprises at least one substantially water insoluble film forming agent, at least one film plasticiser agent, at least one water soluble compound and at least one organic solvent. The ingredients should of course be physiologically compatible and when combined, administered to the skin and allowed to dry 25 the composition forming a flexible, and physiologically compatible porous, skin patch or skin covering film which degrades over time.

The film forming agents that may be used in the present invention include acrylic acid and its derivatives, polyacrylic and its derivatives such as polybutylmethacrylate and 30 polymethacrylic acid, polymethacrylate, ascorbyl palmitate, carbomer, carnauba wax, cellulose derivatives such as cellulose acetate phthalates, rosca mellose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose and related compounds, hydroxypropyl methylcellulose phthalate, hypromellose phthalate, crospovidone and derivatives/related compounds, cetyl alcohol and derivatives, 35 microcystalline wax, poloxamer, polyethylene glycol, polyurethane, polyvinyl acetate, polyvinyl acetate phthalate, polyvinyl alcohol, povidone, silicone rubber and derivatives,

shellac, triglycerides derivatives. These film forming agents are organic solvent soluble, for example, in organic solvents which are dermatological compatible solvents used in dermatological, pharmaceutical and veterinary applications.

5 It is also possible for a number of substantially water insoluble film forming agents to be included within the composition, which when combined and applied to the skin will likewise form a flexible skin patch.

The composition should include at least one film plasticiser agent that will serve to soften 10 the polymer film formed by the film forming agent and to ensure that it is sufficiently flexible that it can move with the skin on the area to which it is applied without cracking and peeling (at least during the intended lifespan of the skin patch). Examples of suitable film plasticiser agents include polybutylphthalate, benzyl benzoate, dibutyl sebacate, dimethyl phthalate, dibutyl phthalate, triacetin, glycol and derivatives thercof, benzyl 15 benzoate, glycerin, mineral oil, lanolin alcohols (such as C₁₋₈ alcohols), petroleum and lanolin alcohols, polyethylene glycol, glycerin, sorbitol, triacetin, triethylene citrate, propylene glycol, chlorbutanol, castor oil and gelatin.

An important aspect of the present invention is that the skin patch formed by use of the 20 composition is porous. This porosity is achieved by including within the composition at least one water soluble compound that will be integrated within the polymer film when applied to the skin. Without limiting the invention, it is believed that the presence of a water soluble compound will, when the film comes into contact with moisture, cause molecules of this compound to leach out of the film, resulting in the forming of windows or pores within 25 the film itself. These pores will allow the passage of gases and water vapour through the skin patch film. In a preferred embodiment of the invention the water soluble compound also has another role within the composition, such as for example as a physiologically active ingredient. Examples of physiologically active ingredients that are also water soluble include antimicrobial quaternary ammonium compounds such as for example cetrimide 30 alkylaryltriaalkylammonium chloride, alkylaryltrimethylammonium chloride, amantanium bromide, benzalkonium chloride, benzethonium chloride, benzododecinium bromide, cetalkonium chloride, cethexonium bromide, cetrimonium bromine, and cetyltrimethylammonium bromide.

35 Compounds such as these will integrate evenly within the film and act immediately on bacteria associated with the effected skin area covered by the film, leaving a multiplicity of

windows or pores within the film, allowing the skin beneath to breathe and perspire, and at the same time preventing the trapping of anaerobic bacteria beneath the film. Quaternary ammonium compounds such as cetrimide are advantageous because they have surfactant action which may assist in binding the film onto the skin to which it is applied. Quaternary 5 ammonium compounds such as cetrimide may also assist to soften and maintain the softness of blood clots with which it will come into contact. This action helps to prevent scabbing of a wound, cut or abrasion, thus facilitating the antimicrobial effects.

Other examples of water soluble compounds that can be incorporated within the composition 10 to aid in formation of pores within the skin patch are antifungal agents such as chlorbutanol, phenol, phenol derivatives such as resorcinol, salicylic acids, acrisorcin, amorolfine, amphotericin, azoles derivatives and related compounds (bifonazole, butoconazole nitrate, chlormidazole, clotrimazole, croconazole, econazole, enilconazole, fenticonazole, fluconazole, flutrimazole, isoconazole, itraconazole, ketoconazole, lanoconazole, 15 miconazole, omoconazole, saperconazole, sertaconazole, sulconazole, terconazole, tioconazole), benzoyl disulphide, bromochlorosalicylanilide, buclosamide, butenafine, candicidicaprylic acid, chlorphenesin, ciclopirox olamine, cilofungin, fentilcor, flucytosine, criseofulvin, hachimycin, haloprogin, hamycin, hydroxystilbamidine isethionate, loflucarban, meparticin, natamycin, nifuroxime, p-nitrophenol, nystatin, pentamycin, 20 propionic acid, protiofate, pyrrolnitrin, sultentine, terbinafine, tolcciclate, tolnaftate, triacetin, undecenoic acid. Water soluble agents are not limited to antimicrobial agents or antifungal agents. Skin conditioners such as ethoxylated lanoline, alcohols (such as C₄ to C₈ alcohols, for example, methanol, ethanol, propanol or isopropanol), and glycerin may be used. Any material that has good solubility in water and slight solubility in volatile organic solvents such 25 as such as C₄ to C₈ alcohols (for example, methanol, ethanol, propanol or isopropanol), acetone, ethyl acetate, dimethyl ether and other polar solvents may also be used.

In order to aid application of the skin patch composition by spraying, the composition will include at least one organic solvent, preferably a volatile organic solvent. By way of 30 example only, one or more solvents may be selected from acetone, ethyl acetate and isopropanol. These solvents are preferred as they may offer some bactericide activity. Other solvents that may be adopted include: alcohols, for example C₁ to C₁₀ alcohols, such as benzyl alcohol, ethanol, methanol, butanol, isobutanol, diacetone alcohol; chlorinated hydrocarbons such as methylene chloride, carbon tetrachloride, trichloroethylene, 35 chlorothene SM; esters such as methyl acetate, ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, amyl acetate, 2-thyl hexyl acetate, duPont DBE, Exxate 500, 700,

900; glycol and ether/ester derivatives, ethylene glycol, PM acetate, butyl cellosolve, Carbitol acetate, butyl Carbitol acetate, Ektapro EEP; hydrocarbons such as toluene, cyclohexene, VM&P naphtha, mineral spirits, Aromatic 100, Aromatic 150, ketones such as acetone, methyl ethyl ketone, methyl butyl ketone; ethers such as dimethyl ether; benzyl benzoate; isopropyl myristate; acetonitrile; ethyl oleate; glycerol, glycofurool (tetraglycol); propylene glycol, polyethylene glycol (PEG); hexane; n-hexane, glycol ethers; methylene chloride; methyl chloride; octyl dodecanol; toluene; trichlorethane; diethyl phthalate; and dibutyl phthalate. These solvents are volatile and, in general, in levels used in dermatological preparations do not cause substantial irritation to the skin, that is, are pharmaceutically acceptable. On application to the skin the solvents rapidly volatilize. A small amount of a non-volatile solvent (for example, less than 2%v/v of total solvent) may be included.

The spray-on skin patch composition having wound treatment application may optionally include one or more physiologically active ingredients, or prodrugs thereof, that may for example be one or more of, or a combination of the following: rapidly-acting antimicrobials (such as cetrimide), long-acting antimicrobials, such as triclosan, benzyl benzoate, dibutyl sebacate, dimethyl phthalate, dibutyl phthalate, triacetin, glycol and derivatives, corticosteroids, pain relieving agents, compounds having antiinflammatory activity, antihistamine, and biologically active peptides or proteins. This list of active agents is not intended to be limiting upon the nature of physiologically active ingredients that can be incorporated within such compositions as any agents that are compatible with the other components of the composition and which can be administered effectively via spraying onto the skin are considered to fall within this aspect. Details of physiologically active ingredient which may be used in this aspect are set out below in relation to the spray patch skin delivery composition aspect of the invention.

By the terms "rapidly-acting" and "long-acting" antimicrobials as used herein it is envisaged that short-acting antimicrobials will effect an anti-microbial activity at the site of application for a period of between about one and about four hours, whereas long-acting antimicrobials will demonstrate activity over a period of from about four hours to about forty eight hours. Activity can be measured by methods routine in the art, that involve taking a swab from a wound site and monitoring microorganism proliferation and viability following exposure to the anti-microbial concerned.

Where the water soluble component of the composition is a physiologically active ingredient, the optional one or more physiologically active ingredient may be the same or different.

5 In accordance with another aspect of the invention there is provided a spray patch skin delivery composition comprising:

(a) at least one substantially water insoluble film forming agent;

(b) at least one film plasticiser agent;

(c) at least one water soluble compound;

10 (d) at least one organic solvent; and

(e) one or more physiologically active ingredient or a prodrug thereof;

the composition forming a flexible, porous and physiologically compatible skin patch when sprayed onto skin and allowed to dry, and which provides transdermal drug delivery.

15 The physiologically active agent or prodrug thereof which may be used in this aspect includes any locally or systemically active agents which are compatible with the porous film of the invention. These agents may be delivered transdermally through the skin without the need for dermal penetration enhancers (which may cause skin irritation or sensitivity). Examples of physiologically active agents or prodrugs thereof include, one or more
20 conveniently classified below by therapeutic class.

Alimentary System

Antidiarrhoeals such as diphenoxylate, loperamide and hyoscyamine.

25 **Cardiovascular system**

Antihypertensives such as hydralazine, minoxidil, captopril, enalapril, clonidine, prazosin, debrisoquine, diazoxide, guanethidine, methyldopa, reserpine, trimetaphan.

Calcium channel blockers such as diltiazem, felodipine, amlodipine, nifendipine, nifedipine and verapamil.

30 Antiarrhythmics such as amiodarone, flecainide, disopyramide, procainamide, mexiletene and quinidine.

Antiangina agents such as glyceryl trinitrate, erythritol tetranitrate, pentaerythritol tetranitrate, mannitol hexanitrate, perhexilene, isosorbide dinitrate and nicorandil.

Beta-adrenergic blocking agents such as alprenolol, atenolol, bupranolol, carteolol, labetalol, 35 metoprolol, nadolol, nadoxolol, oxprenolol, pindolol, propranolol, sotalol, timolol and timolol maleate.

Cardiotonic glycosides such as digoxin and other cardiac glycosides and theophylline derivatives.

Adrenergic stimulants such as adrenaline, ephedrine, fenoterol, isoprenaline, orciprenaline, rimiterol, salbutamol, salmeterol, terbutaline, dobutambe, phenylephrine, 5 phenylpropanolamine, pseudoephedrine and dopamine. Vasodilators such as cyclandelate, isoxsuprine, papaverine, dipyrimadole, isosorbide dinitrate, phentolamine, nicotinyl alcohol, co-dergocrine, nicotinic acid, glyceryl trinitrate, pentaerythritol tetranitrate and xanthinol. Antimigraine preparations such as ergotamine, dihydroergotamine, methysergide, pizotifen and sumatriptan.

10

Drugs affecting blood and haemopoietic tissues.

Anticoagulants and thrombolytic agents such as warfarin, dicoumarol, low molecular weight heparins such as enoxaparin; plasminogen activators such as streptokinase and its active derivatives, t-pA and its derivatives and the like.

15 Haemostatic agents such as aprotinin, tranexamic acid and protamine.

Central nervous system

Analgesics, antipyretics including the opioid analgesics such as buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, alfentanil, sufentanil, hydromorphone, 20 methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, codeine and dihydrocodeine. Others include acetylsalicylic acid (aspirin), paracetamol, and phenazone.

Hypnotics and sedatives such as the barbiturates, amylobarbitone, butobarbitone and pentobarbitone and other hypnotics and sedatives such as choral hydrate, chlormethiazole, 25 hydroxyzine and meprobamate.

Antianxiety agents such as the benzodiazepines, alprazolam, bromazepam, chlordiazepoxide, clobazam, chlorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, nitrazepam, oxazepam, temazepam and triazolam.

30 Neuroleptic and antipsychotic drugs such as the phenothiazines, chlorpromazine, fluphenazine, pericyazine, perphenazine, promazine, thiopropazate, thioridazine and trifluoperazine and the butyrophenones, droperidol and haloperidol and the other antipsychotic drugs such as pimozide, thiothixene and lithium.

35 Antidepressants such as the tricyclic antidepressants amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline, opipramol, protriptyline and trimipramine and the tetracyclic antidepressants such as mianserin and the monoamine oxidase inhibitors such as isocarboxazid, phenelizine, tranylcypromine and moclobemide

and selective serotonin re-uptake inhibitors such as fluoxetine, paroxetine, citalopram, fluvoxamine and sertraline.

CNS stimulants such as caffeine.

Antialzheimer's agents such as tacrine.

5 Antiparkinson agents such as amantadine, benserazide, carbidopa, levodopa, benztrapine, biperiden, benzhexol, procyclidine and dopamine-2 agonists such as S(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin (N-0923).

Anticonvulsants such as phenytoin, valproic acid, primidone, phenobarbitone, methylphenobarbitone and carbamazepine, ethosuximide, methsuximide, phenoxsuximide, 10 sulthiame and clonazepam.

Antiemetics, antinauseants such as the phenothiazines, prochlorperazine, thiethylperazine and 5HT-3 receptor antagonists such as ondansetron and granisetron and others such as dimenhydrinate, diphenhydramine, metoclopramide, domperidone, hyoscine, hyoscine hydrobromide, hyoscine hydrochloride, cleopride and brompride.

15

Musculoskeletal system

Non-steroidal antiinflammatory agents including their racemic mixtures or individual enantiomers where applicable, such as ibuprofen, flurbiprofen, ketoprofen, aclofenac, diclofenac, aloxiprin, aroxen, aspirin, diflunisal, fenoprofen, indomethacin, mefenamic acid, naproxen, phenylbutazone, piroxicam, salicylamide, salicylic acid, sulindac, desoxysulindac, tenoxicam, tramadol and ketorolac.

Additional non-steroidal antiinflammatory agents which can be formulated in combination with the dermal penetration enhancers include salicylamide, salicylic acid, flufenisal, 25 salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzylamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloride, fluprofen, ibufenac, naproxol, fenbufen, cinchophen, diflumidone sodium, 30 fenamole, flutiazin, metazamide, letimide hydrochloride, naxeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, and triflumidale.

Antirheumatoid agents such as penicillamine, aurothioglucose, sodium aurothiomalate, methotrexate and auranofin.

35 Muscle relaxants such as baclofen, diazepam, cyclobenzaprine hydrochloride, dantrolene, methocarbamol, orphenadrine and quinine.

Agents used in gout and hyperuricaemia such as allopurinol, colchicine, probenecid and sulphapyrazone.

5 Hormones and steroids

Oestrogens such as oestradiol, oestriol, oestrone, ethinyloestradiol, mestranol, stilboestrol, dienoestrol, epioestradiol, estropipate and zearanol.

Progesterone and other progestagens such as allyloestrenol, dydrogesterone, lynoestrenol, norgestrel, norethyndrel, norethisterone, norethisterone acetate, gestodene, levonorgestrel, 10 medroxyprogesterone and megestrol.

Antiandrogens such as cyproterone acetate and danazol.

Antioestrogens such as tamoxifen and ciprostanol and the aromatase inhibitors, exemestane and 4-hydroxy-androstenedione and its derivatives.

Androgens and anabolic agents such as testosterone, methyltestosterone, clostebol acetate, 15 drostanolone, furazabol, nandrolone oxandrolone, stanozolol, trenbolone acetate, dihydrotestosterone, 17-alpha-methyl-19-nortestosterone and fluoxymesterone

5-alpha reductase inhibitors such as finasteride, turosteride, LY-191704 and MK-306.

Corticosteroids such as betamethasone, betamethasone valerate, cortisone, dexamethasone, 20 dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide.

25 Further examples of steroidal antiinflammatory agents for use in the instant compositions include cortodoxone, fluoracetone, fludrocortisone, difluorosone diacetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and its other esters, chloroprednisone, clorcortelone, descinolone, desonide, dichlorisone, difluprednate, flucetonide, flumethasone, flumsolide, flucortolone, fluoromethalone, fluperolone, 30 fluprednisolone, meprednisone, methylmeprednisolone, paramethasone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucetonide, flumethasone 35 pivalate, flunisolide acetate, fluperolone acetate, fluprednisolone valerate, paramethasone acetate, prednisolamate, prednival, triamcinolone hexacetonide, cortivazol, formocortal and

nivazol. Pituitary hormones and their active derivatives or analogs such as corticotrophin, thyrotropin, follicle stimulating hormone (FSH), luteinising hormone (LH) and gonadotrophin releasing hormone (GnRH).

Hypoglycaemic agents such as insulin, chlorpropamide, glibenclamide, gliclazide, glipizide, 5 tolazamide, tolbutamide and metformin.

Thyroid hormones such as calcitonin, thyroxine and liothyronine and antithyroid agents such as carbimazole and propylthiouracil.

Other miscellaneous hormone agents such as octreotide.

Pituitary inhibitors such as bromocriptine.

10 Ovulation inducers such as clomiphene.

Genitourinary system

Diuretics such as the thiazides, related diuretics and loop diuretics, bendrofluazide, chlorothiazide, chlorthalidone, dopamine, cyclopenthiazide, hydrochlorothiazide, 15 indapamide, mefruside, meizolothiazide, metolazone, quinethazone, bumetanide, ethacrynic acid and frusemide and potassium sparing diuretics, spironolactone, amiloride and triamterene.

Antidiuretics such as desmopressin, lyppressin and vasopressin including their active derivatives or analogs.

20 Obstetric drugs including agents acting on the uterus such as ergometrine, oxytocin and gemeprost.

Prostaglandins such as alprostadil (PGE1), prostacyclin (PGI2), dinoprost (prostaglandin F2-alpha) and misoprostol.

25 Antimicrobials

Antimicrobials including the cephalosporins such as cephalexin, cefoxitin and cephalothin. Penicillins such as amoxycillin, amoxycillin with clavulanic acid, ampicillin, bacampicillin, benzathine penicillin, benzylpenicillin, carbenicillin, cloxacillin, methicillin, phenethicillin, phenoxytmethylpenicillin, flucloxacillin, mezlocillin, piperacillin, ticarcillin and azlocillin.

30 Tetracyclines such as minocycline, chlortetracycline, tetracycline, demeclocycline, doxycycline, methaerycline and oxytetracycline and other tetracycline-type antibiotics.

Aminoglycosides such as amikacin, gentamicin, kanamycin, neomycin, netilmicin and tobramycin.

Antifungals such as amorolfine, isoconazole, clotrimazole, econazole, miconazole, nystatin, 35 terbinafine, bifonazole, amphotericin, griseofulvin, ketoconazole, fluconazole and flucytosine, salicylic acid, fezatione, ticlatone, tolnaftate, triacetin, zinc, pyrithione and

sodium pyrithione. Quinolones such as nalidixic acid, cinoxacin, ciprofloxacin, enoxacin and norfloxacin. Sulphonamides such as phthalylsulphthiazole, sulfadoxine, sulphadiazine, sulphamethizole and sulphamethoxazole.

Sulphones such as dapsone.

5 Other miscellaneous antibiotics such as chloramphenicol, clindamycin, erythromycin, erythromycin ethyl carbonate, erythromycin estolate, erythromycin glucepate, erythromycin ethylsuccinate, erythromycin lactobionate, roxithromycin, lincomycin, natamycin, nitrofurantoin, spectinomycin, vancomycin, aztreonam, colistin IV, metronidazole, tinidazole, fusidic acid and trimethoprim; 2-thiopyridine N-oxide; halogen compounds, 10 particularly iodine and iodine compounds such as iodine-PVP complex and diiodohydroxyquin; hexachlorophene; chlorhexidine; chloroamine compounds; benzoylperoxide.

Antituberculosis drugs such as ethambutol, isoniazid, pyrazinamide, rifampicin and clofazimine.

15 Antimalarials such as primaquine, pyrimethamine, chloroquine, hydroxychloroquine, quinine, mefloquine and halofantrine.

Antiviral agents such as acyclovir and acyclovir prodrugs, famciclovir, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, saquinavir, indinavir, ritonavir, n-docosanol, tromantadine and idoxuridine.

20 Anthelmintics such as mebendazole, thiabendazole, niclosamide, praziquantel, pyrantel embonate and diethylcarbamazine.

Cytotoxic agents such as plicamycin, cyclophosphamide, dacarbazine, fluorouracil and its prodrugs (described, for example, in *International Journal of Pharmaceutics* 111:223-233 (1994)) methotrexate, procarbazine, 6-mercaptopurine and mucophenolic acid.

25

Antiseptics

Still other antimicrobial or antiseptic agents which may be used include alcohols such as ethanol, isopropanol and methylated spirit; cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetrimide, cetylpyridinium chloride, 30 bisdequalinium diacetate, and dequalinium chloride; bisbiguanides such as chlorhexidine and its salts such as chlorhexidineacetate, and polymeric biguanides such as PMMB; chlorine or chlorine containing agents such as chloramine, sodium dichloroisocyanurate and sodium hypochlorite; dyes such as acridine derivatives, brilliant green, crystal violet, magenta and malachite green; iodophores such as providone-iodine; mercurials such as 35 chiomersal and mercurochrome; oxidising agents such as hydrogen peroxide, peracetic acid

and potassium permanganate; phenoxyethanol; phenethyl alcohol; and phenols such as chlorocresol, chloroxylenol, cresol, chlorophenol (triclosane), hexachlorophane and phenol.

Metabolism

5 Anorectic and weight reducing agents including dexfenfluramine, fenfluramine diethylpropion, mazindol and phentermine.
Agents used in hypercalcaemia such as calcitriol, dihydrotachysterol and their active derivatives or analogs.

10 Respiratory system

Antitussives such as ethylmorphine, dextromethorphan and pholcodine.
Expectorants such as acetylcysteine, bromhexine, emetine, guaiphenesin, ipecacuanha and saponins.
Decongestants such as phenylephrine, phenylpropanolamine and pseudoephedrine.
15 Bronchospasm relaxants such as ephedrine, fenoterol, orciprenaline, rimiterol, salbutamol, sodium cromoglycate, cromoglycic acid and its prodrugs (described, for example, in *International Journal of Pharmaceutics* 7:63-75 (1980)), terbutaline, ipratropium bromide, salmeterol and theophylline and theophylline derivatives.

20 Allergy and immune system

Antihistamines such as meclozine, cyclizine, chlorcyclizine, hydroxyzine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine, diphenylamine, doxylamine, mebhydrolin, mepyramine, pheniramine, tripolidine, azatadine, diphenylpyraline, methdilazine, terfenadine, astemizole, loratadine and cetirizine.
25 Local anaesthetics such as bupivacaine, amethocaine, lignocaine, cinchocaine, dibucaine, mepivacaine, prilocaine and etidocaine.
Stratum corneum lipids, such as ceramides, cholesterol and free fatty acids, for improved skin barrier repair (Man, *et al.*, *J. Invest. Dermatol.*, 106(5):1096, 1996).
Neuromuscular blocking agents such as suxamethonium, alcuronium, pancuronium,
30 atracurium, gallamine, tubocurarine and vecuronium.
Smoking cessation agents such as nicotine, bupropion and ibogaine.
Insecticides and other pesticides which are suitable for local or systemic application.
Dermatological agents, such as vitamins A and E, vitamin E acetate and vitamin E sorbate.
Allergens for desensitization such as house dust mite allergen.
35 Nutritional agents, such as vitamins, essential amino acids and essential fats.
Keratolytics such as the alpha-hydroxy acids, glycolic acid and salicylic acid.

Psychicenergisers, such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

Anti-acne agents such as containing isotretinoin, tretinoin and benzoyl peroxide.

Anti-psoriasis agents such as containing etretinate, cyclosporin and calcipotriol.

5 Anti-itch agents such as capsaicin and its derivatives such as nonivamide (Tsai, *et al*, *Drug Dev. Ind. Pharm.*, 20(4):719, (1994)).

Anticholinergic agents, which are effective for the inhibition of axillary sweating and for the control of prickly heat. The antiperspirant activity of agents such as methatropine nitrate, propantheline bromide, scopolamine, methscopolamine bromide, and the new class of soft 10 antiperspirants, quaternary acyloxymethyl ammonium salts (described, for example, by Bodor *et al*, *J. Med. Chem.*, 23:474 (1980) and also in United Kingdom Specification No 2010270, published 27 June 1979).

Other physiologically active peptides and proteins, small to medium-sized peptides, for example, vasopressin and human growth hormone.

15

The physiologically active agent or a prodrug thereof is preferably present at a concentration which is soluble in the delivery system, but after evaporation of solvent may precipitate forming drug depots in the porous film.

20 A concentration gradient is believed, without wished to be bound by theory, to be the means through which biologically agents or prodrugs thereof pass through the skin. It is believed that the porous nature of the patch or film which forms on the skin provides a depot like effect with foci of highly concentrated biologically active agents. The concentration gradient so formed is believed to force the agent across the skin. A continuous delivery may 25 result. It is also believed that the porous nature of the film, which allows the passage of gases and water vapour, and avoids issues of skin irritation associated with films/patches applied to the skin for transdermal application.

An advantage of the compositions according to the present invention is that they may 30 disintegrate over a period of time so that peeling or scrubbing off of the film may be unnecessary. The time frame of such disintegration is governed by the choice of the film forming agent and the degree of interruption within the film that has been caused by addition to the composition of a water soluble compound. By selection of these components the lifespan of the skin patch can be varied as a design feature of the composition. For example, 35 the patch may disintegrate over say a twenty four or forty eight hour time period.

In another aspect of the invention there is provided a spray patch transdermal drug delivery system which comprises at least one physiologically active agent or pro-drug thereof in a water insoluble, porous, film structure containing drug depots.

- 5 The drug delivery system is adapted to transport the physiologically active agent across a dermal surface or mucosal membrane of an animal, including a human. The device is of low toxicity to, and is exceptionally well tolerated by the dermal surface or mucosal membrane of the animal.
- 10 The present invention also provides a method for administering at least one systemic or locally acting physiologically active agent or prodrug thereof to an animal which comprises applying an effective amount of the physiologically active agent in the form of a composition or a drug delivery system according to the present invention.
- 15 Preferably the animal is a human but the invention also extends to the treatment of non-human animals, such as companion animals (for example, dogs and cats), domestic animals, for example, cows/cattle, sheep, horses, goats, pigs and the like, and birds.

Surprisingly, the compositions and device of the invention enhances the absorption of active agents and prodrugs thereof through the skin and mucous membranes while avoiding the significant pharmacological disadvantages and toxicities of prior art approaches.

In the compositions and drug delivery systems according to the various aspects of the invention a pharmaceutical compounding agent, cosolvent, surfactant, emulsifier, 25 antioxidant, preservative, stabilizer, diluent or a mixture of two or more of said components may be incorporated as is appropriate to the particular route of administration and dosage form. The amount and type of components used should be compatible with the polymer film structure. A cosolvent, or other standard adjuvant such as a surfactant, may be used to maintain a physiologically active agent, or prodrug, thereof in a solution or suspension at the 30 desired concentration.

The pharmaceutical compounding agents can include paraffin oils, esters such as isopropyl, myristate, ethanol, silicone oils and vegetable oils. These are preferably used in the range of greater than 1%. Surfactants such as ethoxylated fatty alcohols, glycerol monostearate, 35 phosphate esters, and other commonly used emulsifiers and surfactants preferably in the range of 0.1% to 1% may be used, as may be preservatives such as hydroxybenzoate esters

for preservation of the compound preferably in amounts of 0.01% to 0.5%. Typical cosolvents and adjuvants may be ethyl alcohol, isopropyl alcohol, acetone, dimethyl ether and glycol ethers such as diethylene glycol monoethylether. These may be used in amounts of 1% to 90%.

5

When a pharmaceutical compounding agent, cosolvent, surfactant, emulsifier, antioxidant, preservative, stabilizer, diluent or a mixture of two or more of said components is used, these must be compatible with the ability of the system to become touch-dry after application.

10

The non-aerosol spray-on skin patch compositions according to the invention can conveniently be applied by means of a positive displacement metered dose hand pump, preferably having a lock down device that will seal the entry of air into the can. The organic solvents included within the composition will serve to clean the spraying nozzle and prevent 15 build up of polymer film there within. By using the metered dose pump it is possible to deliver a precise amount of film onto the skin, and this in association with knowledge of the concentration of physiologically active ingredients within the composition can serve to ensure that the level of active administered is tightly controlled. Other variables that will need to be considered in the control of active ingredient administration (especially in the 20 situation where the dose application is not metered) include the area of skin contacted with the composition, and the length of time of skin contact. Naturally, it will be well within the capabilities of a skilled physician to determine the effective amount of the physiologically active ingredient that needs to be applied, as well as the number of applications required, and alter the variables mentioned above in order to ensure the correct level of administration.

25

Factors that would be apparent to a skilled clinician such as the height, weight, age, sex and general state of health of the patient concerned may also need to be considered, in determining the correct dose for a specific patient. For example, dosage ranges may include an active ingredient in the range from about 0.01 ng to 500 mg, such as 0.01 mg to 100 mg, for example 0.1 mg to 75 mg or 1 mg to 300 mg per dose.

30

Proportions of the components, according to various aspects of this invention, include, but are not limited to, 1% to 50% w/w film forming agent, 0.1% to 20% w/w film plasticiser agent, 0.01% to 10% w/w water soluble compound or compounds, and 30% to 90% w/w organic solvent or solvents.

35

In one embodiment the skin delivery composition may comprise a non-aerosol spray-on skin patch composition comprising:

0.01% to 10% w/w of one or more water soluble compounds
0.01% to 10% w/w of one or more physiologically active ingredient/s
5 1% to 50% w/w of polymethacrylic acid
0.1% to 20% w/w of polybutylphthalate
0% to 90% w/w of isopropanol
0% to 90% w/w of acetone
ethylacetate up to 100% w/w,

10 the composition forming a flexible, porous and physiologically compatible skin patch when sprayed onto skin and allowed to dry.

Other physiologically acceptable carriers, diluents, solvents or excipients may also be included within the composition, as is well known in the art of pharmaceutical formulation.

15 Details of such materials are provided within *Max Remington's Pharmaceutical Sciences*, 17th Edition, Mack Publishing Co, Easton Pennsylvania, USA, the disclosure of which is included herein in its entirety, by way of reference.

The compositions according to the present invention may be used in methods of treatment, 20 such as, for the treatment of skin wounds, fungal infection, healing after plastic surgery, eczema, bacterial infection in or on the skin and or associated with skin wounds, athlete's foot, skin ulceration, burns, scalds, insect bites, local analgesia, itching, pain, and other method aspects as herein described.

25 Pain treated herein may be rheumatic pain (such as joint and muscle pain), pain associated with skin ulcers, pain associated with anal fissure and the like.

Administration may be to the site of injury or condition, or remote thereto.

30 Further aspects of the present invention will be explained in the following non-limiting Examples.

EXAMPLES

Example 1

35 A composition is prepared as follows:

a non-aerosol spray-on skin patch composition comprising:

0.05% w/w of centrimide
0.07% w/w of triclosane
0.6% w/w of chlorbutanol
10% w/w of polymethacrylic acid
5 1.2% w/w of polybutylphthalate
4% w/w of isopropanol
24% w/w acetone
ethylacetate up to 100% w/w.

10 **Example 2**

Continuous release of antimicrobial actives from the applied composition of Example 1

Sample

One litre of the compositions according to Example 1 (Spray On Antimicrobial Bandage) in a Nalgene bottle was received for validation. The bottle was labelled "Ref. BX258

15

Method

The procedure was based on the Australian Standards AS1157.1 and .2, 1998 incorporating the microbes stipulated in the BP Preservative Efficacy Test.

20 One mL of the sample was used to saturate a membrane pad. Once dry, the pad was then placed onto the surface of agar plates containing a lawn culture of the following microorganisms:

	<u>Medium</u>	<u>Micro-organism</u>	<u>Challenge population/plate</u>
25	*TSA	<i>Escherichia coli</i>	3×10^8
	TSA	<i>Staphylococcus aureus</i>	3×10^8
	*SDA	<i>Candida albicans</i>	3×10^6
	SDA	<i>Aspergillus niger</i> (spores)	1×10^7

(*TSA = Tryptone Soya Agar, SDA = Sabouraud Dextrose Agar)

30

Positive and negative controls were performed in parallel.

The TSA plates were incubated at 37°C for three days and the SDA plates were incubated at 25°C for five days.

Results

Where G = Growth evident on pad

NG = No growth evident on pad

5 After incubation growth was noted on the plate, pad and under the pad and any zone of inhibition was measured.

		<u>Pad G or NG/</u>	<u>Zone of Inhibition</u>
	<u>Micro-organism</u>		
10	<i>E.coli</i> :	NG/0.5 mm	
	<i>S.aureus</i> :	NG/0.5 mm	
	<i>C.albicans</i> :	NG/0.6 mm	
	<i>A.niger</i> :	NG/no zone of inhibition	
15			

Findings

1. All surfaces coated with Medico Spray-On Bandage prevented microbial growth on the agar in contact with the product. This was irrespective of whether the field was -
 - (a) *E.coli*, a Gram-negative bacterial rod.
 - (b) *S.aureus*, a Gram-positive bacterial coccus
 - (c) *C. albicans*, a pathogenic yeast
 - (d) *A.niger*, a spore-bearing mould
2. A zone of inhibition was noted in challenges (a) to (c) above, although this effect is not deemed necessary for the product; i.e - the spray-on bandage need only prevent growth in the region sprayed which covers the open wound. Efficacy beyond the zone of broken skin is independent of the functional application of the product.
3. Controls were in line with expectation, that is, uninhibited bacterial growth took place.

30 Example 3**Effect of Example 1 Composition on Contusion**

This example shows that the composition of Example 1 is a transparent, antiseptic, waterproof, washable "Spray-on-Bandage" having application in cuts, minor wounds and

abrasions. Effectiveness in an artificial contusion in the rabbit was studied. The following results were obtained.

1. The date of testing

13 June 1999 until 23 July 1999

5 2. The testing materials and test method

1) Testing animal: Rabbit.

2) Testing composition: Example 1 composition.

3) The two artificial wounds have been made on the centre of the back of the rabbits.

Observations were taken after contusion on treated and non-treated animals.

10 a) The operative method to make the artificial contusion

Hair has been shaved on the centre part of rabbit's back, and then the intrusion of 3 cm² made by strong abrasion to the skin with sandpaper.

b) Observation

15 The visible observation to the naked eye has been made on the first day, the second day, the fifth day and the tenth day respectively after the operation. On the tenth day the rabbit has been killed so that the inspection of pathological tissue can be made.

3. Result

1) Visible observation

The visible change of the operated part is shown in the Table 1 below.

20

Table 1

	Observation items	1 st day	2 nd day	5 th day	10 th day
Treatment with Example 1	Area of operated part (cm ²)	3	3	3	3
	Redness	-	-	-	-
	Scabbing	-	-	-	-
	Hypertrophy	+	-	-	-
Without treatment	Area of operated part (cm ²)	1.7	1.7	1.3	1.0
	Redness	-	-	-	-
	Scabbing	+	+	+	+
	Hypertrophy	-	+	++	+++

2) The inspection of the pathological tissue of the operated part

Pathological tissue analysis is shown in Table 2

25

Table 2

	Treated with Example 1	Untreated object
Epidermis	normal	Increase
Papilla	normal	Extend
Papilla layer	normal	Increase
Scabbing formation	none	Exist
Cell infiltration	small	Big

4. Conclusion

1) As far as the visible observation is concerned, the untreated wound has scabbing on the first day after operation. Compression from the surrounding tissue is visible on the operated part. Furthermore, hypertrophy has been continuous.

5 On the other hand, as to the wound treated with Example 1, we were unable to observe any atrophy on the operated part due to the performance of the composition.

10 2) Pathological tissue analysis of the untreated wound shows on the operated part, as to chronic dermatitis, increase of epidermis, increase of papilla layer, and cell infiltration.

On the contrary, as far as the specimen treated with Example 1 is concerned, no significant abnormality has been observed except for the slight cell infiltration.

15 15 Full protection of wounds as well as the regeneration of normal tissue is observed with the treatment composition.

Plastic surgery tissue abrasions may be treated with the composition. Other examples of application include bandages for the wounds to cattle and other animals.

The trial results indicate the composition promotes rapid healing of surface abrasions and surgical wounds.

20 25 The applied compositions of Example 1 effectively acts as a true pseudoskin and as such allows rapid sub-membrane proliferation of an epithelial cellular layer. In this manner the

contused surface is rapidly reepithelialised with associated minimisation of epithelial cellular hypertrophy and contracture.

Example 4

5 A semipermeable Wound Spray, Example 1 Bandage for Dogs and Cats

The example 1 spray has been used in the treatment of wounds, dermatitis (eczema madidans), abscesses, furunculosis, otitis external and postoperative wounds. Before treatment with Example 1 composition, samples from the various conditions were taken for laboratory determination of bacteria.

10

Three days after treatment with Example 1 composition which formed a skin patch or bandage the treated area was evaluated for colour, sensibility, humidity and pus as well as water repellent quality, adhesiveness and scale production.

15 Ninety three animals, eighty dogs and thirteen cats, were treated with the Example 1 bandage.

The objective of the study was to ascertain:

1. Will it be possible for the Example 1 bandage to protect the wound and avoid water penetration.
- 20 2. Will the Example 1 bandage be able to stop the irritation and red erythema, characteristic of acute wounds and eczema madidans.

25 **Table 3**
Number of animals and age distribution in the test

Diagnose	Number
Dermatitis	13
Flegmone, absces	7
Furunculose	4
Operating	55
Otitis externa	8
Vulnus inc., morsum	6

Table 4
The results of the bacteriological determination

5

Cultivation results	Number
g+ and g- Staphylococcus	21
g-Clostridium Staphylococcus	18
Haemolytic Staphylococcus	18
Proteus	2
Anaehaemolytic g-Staphylococcus	3
Staphylococcus faecalis	1
Klebsiella	1
Yeast g-Staphylococcus	5
Sterile after forty eight hours	30

Table 5

The result of the clinical examination three days after treatment with Example 1 bandage.

10

	Yes	No	%
Colour	6	87	7
Sensibility	0	93	0
Smell	1	92	1
Humidity	22	71	24
Pus	5	88	5
Water-repellent	90	3	97
Viscosity	0	93	0
Scate production	3	90	3

Conclusion

The use of Example 1 bandage for minor cuts and wounds has shown that it relieves the erythema in 93 % of the cases and that it has a water-repellent effect in 97 %.

15 From the results obtained Example 1 bandage obviously has a good antiseptic quality for treatment of minor cuts, post-operative wounds, dermatitis and abscesses.

Example 5

Spray On Antifungal Bandage for athlete foot caused by Tinea spp.

20 Most common non-fatal skin infections are cause by various bacterial and fungi tinea pedis, tinea cruris, tinea corporis and cutaneous candida albicans. Miconazole is one of the common

antifungal agents against such infections. Miconazole appears to act on cell wall and membranes, inducing permeability changes that alter the ionic micromolecular composition of the affected cells. The recommended product strength containing miconazole (for example, Daktarin by Janssen – Cilag) is 2% as powder, tincture or cream applied twice 5 daily to the infected area.

The difficulty of using an antibacterial / antifungal cream, tincture or powder for tinea infection is that the medication cannot adhere to the infected area. This is particularly true if the infection is on the foot (for example, athlete foot). This gives rises to unsatisfactory 10 results and repeated infections.

The following example product formulation demonstrated the usefulness of the spray on patch delivery system, which greatly improves the efficacy of miconazole and the likes of antifungal agents. The formulation also contains Chlorbutanol, which is a traditional anti 15 bacterial, and anti fungal agent the use of which is well documented in various pharmacopoeiae.

The spray on medicated patch adheres to surface of infected skin over a long period of time (about twenty four hours) delivering active ingredients continuously to the infected surface. 20 In addition, the spray can be used to fungal proof footwear to prevent further re-infections. Product strength compared to other commercial product (for example, Daktarin) is halved (from 2% to 1%) and dosage rate is also halved to daily application only (from twice daily to once daily).

25 Spray On Antifungal Bandage for athlete foot caused by *Tinea* spp.

Formulae

Miconazole USP	1.0% w/v	Active, antifungal
Chlorbutanol BP / Eur.P	0.6% w/v	Active, antibacterial/antifungal
Phenol BP/ Eur.P	0.2% w/v	Preservative
30 Poly methacrylate USNF	10.0% w/v	Film former
Poly butyl Phthalate BP /Eur.P	1.0% w/v	Film softener

Isopropanol USP	24%w/v	Solvent
Acetone BP / Eur.P	24%w/v	Solvent
Ethyl Acetate USP	40.7%w/v	Solvent
Total	100%w/v	

5

Method of manufacturing:

Dissolve miconazole and chlorbutanol in isopropanol, phenol, acetone and ethyl acetate. Add in Poly butyl phthalate. Add in Poly methacrylate with gentle stirring. Pack in spray apparatus.

10

Direction for use:

The spray on medication adheres to skin effectively over twenty four hours. Spray on affected area to ensure adequate cover. Used as continuos release antifungal spray once daily. To prevent reinfection, spray into foot ware daily during treatment and thereafter at 15 least once weekly for six months.

A twenty five year old female used the above spray after repeatedly failed to eradicate the fungal problem on her right foot for over five years. Before application, the area was ulcerated, weeping and itchy.

20

The miconazole / chlorbutanol spray on bandage was used daily for five days. Her foot wear was fungal proofed by spraying the same product into the inside of the shoes once daily for five days. After five days, the infected area was visibly reduced. The use of the miconazole spray was stopped. After two weeks the area was clear of infections (no longer weeping, nor 25 cracked, nor itchy and skin healed quite well). After the initial treatment, no incidence of reinfection was reported during the next six months.

A fifty five year old male also used the above spray for five days after failure to control severe fungal problem on the right foot for over ten years. Previous medications including 30 iodine tincture, Daktarin cream, salicylic acid ointment and Nizoral cream.

The miconazole / chlorbutanol spray on patch was used daily for five days. The foot wear was fungal proofed by spraying the same product into the inside of the shoes once daily for five days. After five days, the infected area was visibly reduced. Skin lesions starts to heal there after. The use of the miconazole / chlorbutanol spray was continued for another five days and then stopped. After two weeks the area was clear of infections (no longer weeping, bleeding, cracked, or itchy). After the initial treatment, no incidence of reinfection was reported during the next six months. All footwear was fungal proof by spraying into footwear once weekly for about six months.

10 Example 6

Spray on Betamethasone bandage for allergic skin conditions, eczema and psoriasis

Betamethasone is a corticosteroid indicated for treatment of allergic skin disorders. The product is marketed under the trade name of Betnovate™ as cream, ointment or gel containing betamethasone 0.05% to 0.1% strength. Dosage application is up to four times daily.

It is a well known practice in Australian hospitals that after applying the Betnovate™ cream, gel or ointment, efficacy can be improved by wrapping the area in "Glad Wrap"™ (a thin polymer film) to enhance absorption and prolong drug contact.

20

The following formulation is capable of replacing the "Glad Wrap" practice efficiently. Application is also reduced from up to four times daily to once daily. Formulation also contains an effective antimicrobial agent that treat and prevents bacterial or fungal infections in case of weeping wound or ulcers.

25

Spray on Betamethasone bandage for allergic skin conditions, eczema and psoriasis

Betamethasone Valerate BP/Eur.P 0.12%w/v Active anti-inflammatory

Chlorbutanol BP / Eur.P 0.6%w/v Active antimicrobial agent

Triclosan (Ciba Geigy

30 Irgasan DP300) 0.1%w/v Preservative

Poly methacrylate USNF	10.0%w/v	Film former
Poly butyl Phthalate BP / Eur.P	1.0% w/v	Film softener
Isopropanol USP	24%w/v	Solvent
Acetone BP / Eur.P	24%w/v	Solvent
5 Ethyl Acetate USP	40.7%w/v	Solvent
Total	100%w/v	

Recommended dosage:

Apply once daily to the affected area for treatment of eczema, psoriasis and allergic skin
10 conditions.

Method of manufacture:

1. Dissolve betamethasone in the mixture of solvents. Add in Triclosan and Chlorbutanol.
2. Add Poly butyl phthalate then Poly methacrylate with gentle stirring.
- 15 3. Pack in airtight aluminum cans and attach actuator and spray nozzle.

Example of use:

A twenty three year old female who suffers both eczema and psoriasis badly since birth has used Betnovate Cream on and off to relieve the skin irritation due to her condition. Her skin affliction was particularly bad during period of stress. She tried the formulated
20 Betamethasone spray on bandage for two weeks prior to her university examination and found her condition is much improved. Symptomatic relieve was achieve within forty eight hours. Relieve of itch and weeping due to constant scratching was fast and effective. She only requires to use the spray once daily at night instead of morning and night. She can wear the betamethsone spray bandage to shower without having to repeat application. The
25 affected area heals well particularly where it is not practical to put a bandage on top to prevent clothes scratching on the affected area.

Example 7

Spray on Mepyramine Antihistamine Adhesive Patch – a first aid treatment for burns,
30 scalds, insect bites, antipruritic and local analgesic application in all conditions characterized by intense itching or pain.

Mepyramine is a well known, well tried and well used antihistamine. Over a hundred medications contain mepyramine as one of its major ingredients.

Spray on Mepyramine Antihistamine Adhesive Patch

5	Mepyramine Maleate BP/Eur.P	2.0%w/v	Active antihistamine
	Chlorbutanol BP / Eur.P	0.6%w/v	Active antimicrobial agent
	Triclosan (Ciba Geigy Irgasan DP300)	0.1%w/v	Preservative
	Poly methacrylate USNF	10.0%w/v	Film former
	Poly butyl Phthalate BP / Eur.P	1.0% w/v	Film softener
10	Isopropanol USP	24%w/v	Solvent
	Acetone BP / Eur.P	24%w/v	Solvent
	Ethyl Acetate USP	40.7%w/v	Solvent
	Total	100%w/v	

15 Method of Manufacture:

1. Dissolve Mepyramine maleate in the mixture of solvents. Add in Triclosan and Chlorbutanol.
2. Add Poly butyl phthalate then Poly methacrylate with gentle stirring.
3. Pack in airtight aluminum cans and attach actuator and spray nozzle.

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A group of boy scouts and parents used the Spray on Mepyramine Antihistamine Adhesive Patch during recent camping. General observation from adults indicated that the formulation relieved symptoms of insect bites fast and efficiently. In one occasion, a twelve year old boy scout was mildly burned by camp fire on the back of the hand while roasting 25 marshmallow. After one application, pain was quickly relieved and no blister formed. It was indicated that the Mepyramine antihistamine spray on bandage also formed a protective cover for the wound and was waterproof. The bandage remained on skin even after swimming and self disintegrated in about twenty-four hours.

Example 8

Further compositions are prepared as follows:

(A) Chlorhexidine acetate 0.5% w/w

5 0.07% w/w of triclosane
0.6% w/w of chlorbutanol
10% w/w of polymethacrylic acid
1.2% w/w of polybutylphthalate
4% w/w of isopropanol
10 24% w/w acetone
ethylacetate up to 100% w/w

(B) Phenoxyethanol 2% w/w

0.07% w/w of triclosane
15 0.6% w/w of chlorbutanol
10% w/w of polymethacrylic acid
1.2% w/w of polybutylphthalate
4% w/w of isopropanol
24% w/w acetone
20 ethylacetate up to 100% w/w

(C) Phenethyl alcohol 2%

0.07% w/w of triclosane
0.6% w/w of chlorbutanol
25 10% w/w of polymethacrylic acid
1.2% w/w of polybutylphthalate
4% w/w of isopropanol
24% w/w acetone
ethylacetate up to 100% w/w

Claims

1. A non-aerosol spray-on skin patch composition comprising:
 - a) at least one substantially water insoluble film forming agent;
 - 5 b) at least one film plasticiser agent;
 - c) at least one water soluble compound; and
 - d) at least one organic solvent;the composition forming a flexible, porous and physiologically compatible skin patch when sprayed onto skin and allowed to dry.
- 10 2. The composition according to claim 1 wherein the at least one water soluble compound comprises at least one physiologically active ingredient.
- 15 3. The composition according to claim 2 wherein the at least one physiologically active ingredient is an antimicrobial agent and/or an antifungal agent.
4. The composition according to either claim 3 wherein the antimicrobial agent is a quaternary ammonium compound.
- 20 5. The composition according to claim 4 wherein the quaternary ammonium compound is selected from cetrimide, alkylaryltriaalkylammonium chloride, alkylaryltrimethylammonium chloride, amantanium bromide, benzalkonium chloride, benzethonium chloride, benzododecinium bromide, cetalkonium chloride, cethexonium bromide, cetrimonium bromine, and cetyltrimethylstearylammnonium bromide.
- 25 6. The composition according to claim 5 wherein the quaternary ammonium compound is cetrimide.
- 30 7. The composition according to claim 3 which comprises a water soluble antimicrobial agent and a water soluble antifungal agent.
8. The compound according to any one of claims 7 wherein the antimicrobial agent is a quaternary ammonium compound and the antifungal agent is selected from chlorbutanol, phenol, phenol derivatives, salicylic acids, arisoran, amorolfine, amphotericin, azole derivatives and related compounds, benzoyl disulphide,
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bromochlorosalicylanilide, buclosamide, butenafine, candicidicaprlyic acid, chlorphenesin, ciclopirox olamine, cilofungin, fentichlor, flucytosine, criseofulvin, hachimycin, haloprogin, hamycin, hydroxystilbamidine isethionate, loflucarban, meparticin, natamycin, nifuroxime, p-nitrophenol, nystatin, pentamycin, propionic acid, protiofate, pyrrolnitrin, sultentine, terbinafine, tolciolate, tolnaftate, triacetin, and undecenoic acid.

- 5 9. The compound according to claim 8 wherein the antifungal agent is chlorbutanol.
- 10 10. The composition according to claim 1 which additionally comprises at least one physiologically active ingredient.
- 15 11. The composition according to claim 10 wherein the at least one physiologically active ingredient is selected from an antifungal, an antimicrobial, an antiseptic, an antiparasitic, a nicotine, a cortico steroid, a pain relieving agent, a cardiac dilater, a cardiac stimulant, an antihistamine, an anti-inflammatory, an anti blood clotting agent, a growth hormone, a sex hormone, or drugs commonly used for diseases in the alimentary system, central nervous system, musculoskeletal system, genitourinary system allergy and immune system, respiratory system, or a biologically active peptide or protein.
- 20 12. The composition according to claim 11 wherein the at least one physiologically active ingredient is triclosane.
- 25 13. The composition according to claim 1 wherein the film forming agent is selected from polymethacrylic acid, polybutyl methacrylate and polyacrylic acid.
- 30 14. The composition according to claim 1 wherein the film plasticiser agent is polybutylphthalate.
15. The composition according to claim 1 wherein the organic solvent is selected from isopropanol, acetone and ethylacetate.
- 35 16. A spray patch skin delivery composition providing:
 - (a) at least one substantially water insoluble film forming agent;
 - (b) at least one film plasticiser agent;

(c) at least one water soluble compound;

(d) at least one organic solvent; and

(e) one or more physiologically active ingredients or a prodrug thereof ;

the composition forming a flexible, porous and physiologically compatible skin patch
5 when sprayed onto skin and allowed to dry, and which breaks down or disintegrates
over a time period on skin, and which provides transdermal drug delivery.

17. The composition according to claim 16 wherein the physiologically active ingredient
or a further physiologically active ingredient is selected from an antifungal, an
10 antibacterial, an antiparasitic, a nicotine, a cortico steroid, a pain relieving agent, a
cardiac dilater, a cardiac stimulant, an antihistamine, an antiinflammatory, an anti
blood clotting agent, a growth hormone, a sex hormone, or drugs commonly used for
the diseases in the alimentary system, central nervous system, musculoskeletal system,
15 genitourinary system allergy and immune system, respiratory system, or a biologically
active peptide or protein.

18. A non-aerosol spray-on skin patch composition comprising:
0.01% to 10% w/w of at one or more water insoluble compounds
0.01% to 10% w/w of one or more physiologically active ingredient/s
20 1% to 50% w/w of polymethacrylic acid
0.1% to 20% w/w of polybutylphthalate
0% to 90% w/w of isopropanol
0% to 90% w/w of acetone
ethylacetate up to 100% w/w,
25 the composition forming a flexible, porous and physiologically compatible skin patch
when sprayed onto skin and allowed to dry.

19. The composition according to claim 18 comprising:
0.05% w/w of centrimide
30 0.07% w/w of triclosane
0.6% w/w of chlorbutanol
10% w/w of polymethacrylic acid
1.2% w/w of polybutylphthalate
4% w/w of isopropanol
35 24% w/w acetone
ethylacetate up to 100% w/w.

20. A method of improving wound healing or administering a physiologically active ingredient to a patient in need of such treatment comprising applying to a wound or to skin of the patient an effective amount of a composition according to claim 1 or claim 5 16.
21. A method for the treatment of skin wounds, fungal infections, eczema, bacterial infections in or on the skin and/or associated with skin wounds, athlete's foot, skin 10 ulceration, burns, scalds, insect bites, allergic skin diseases, psoriasis, itching and pain, which comprises administering to the skin a composition according to claim 1 or 16.

ABSTRACT

5 Non-aerosol spray-on skin patch compositions as described comprising at least one substantially water insoluble film forming agent, at least one film plasticiser agent, at least one water soluble compound, and at least one organic solvent, the composition forming a flexible, porous and physiologically compatible skin patch when sprayed on to skin and allowed to dry. Also described are methods of improving wound healing by administering a
10 physiologically active ingredient to a patient in need of such treatment.